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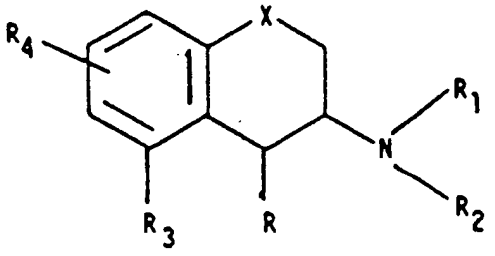
(54) Title: NEW CHROMAN AND THIOCHROMAN DERIVATIVES



(I)

(57) Abstract

Compounds of formula (I), processes for their preparation, pharmaceutical preparations, use of and method of treatment of disorders in CNS by using compounds of formula (I).

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New chroman and thiochroman derivatives

Description

Field of the Invention

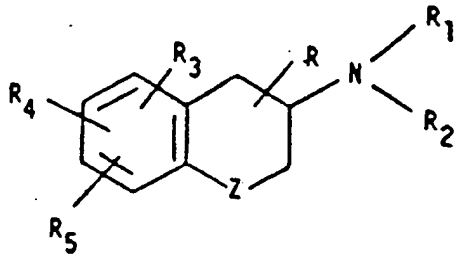
The present invention relates to new substituted-3-amino-chromans and thiochromans, enantiomers and salts thereof, processes for their preparation, pharmaceutical compositions containing said therapeutically active compounds as well as new intermediates useful in the preparation of the therapeutically active compounds and to the use of said active compounds in therapy.

An object of the invention is to provide compounds for therapeutic use, especially compounds having a therapeutic activity via the central nervous system (CNS). A further object is to provide compounds having a selective effect on the 5-hydroxy-tryptamine receptors in mammals including man.

Prior art

Therapeutically useful 3-amino-dihydro-[1]-benzopyran and benzothiopyran having effect on 5-hydroxy tryptamine neurons in mammals are disclosed in EP 0222 996.

These compounds are defined by the formula



wherein Z is O or S;

R is hydrogen or loweralkyl;

R_1 is hydrogen, loweralkyl or arylloweralkyl;

R_2 is hydrogen, loweralkyl or arylloweralkyl;

or R_1 and R_2 together form a ring with 4 - 6 carbon atoms;

R_3 is hydrogen, hydroxy, loweralkoxy, aryllower-alkoxy, acyloxy or aryloxy when Z is S and R_3 is hydroxy, loweralkoxy, arylloweralkoxy, acyloxy or aryloxy when Z is O and R_3 is in 5- or 8-position when Z is O;

R_4 and R_5 are independently hydrogen, lower alkyl or halogen, and mono- or di-S-oxide thereof when Z is S, and pharmaceutically acceptable salts thereof.

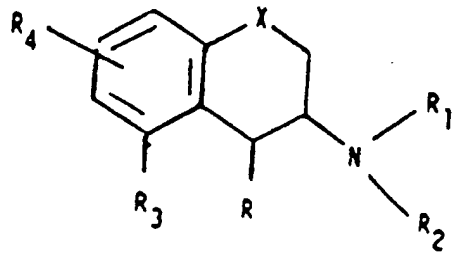
3-Chromanamine hydrochlorides with two alkyl groups in the aromatic ring having central stimulating activities are described in J. Med. Chem. 15, p. 863-65 (1972).

Disclosure of the Invention

The object of the present invention is to obtain new compounds which have a high affinity to the 5-hydroxy-tryptamine receptors in the central nervous system at the same time as they act as agonists, partial agonists or antagonists on the serotonin receptors.

Thus, a group of new compounds of the formula I of the present invention as well as the enantiomers and salts thereof are useful in therapeutic treatment of 5-hydroxy-tryptamine mediated states and disorders such as depression, anxiety, anorexia, senile dementia, Alzheimer's disease, migraine, termoregulator and sexual disturbances. Further aspects of the invention are related to the use of the compounds, enantiomers and salts thereof in pain control and in modulation of the cardiovascular system.

Thus, the invention provides compounds of the formula



I

I

wherein

$(O)_p$
‖
X is O or S;

p is an integer 0, 1 or 2;

R is hydrogen, fluoro or C_1-C_6 alkyl;

R_1 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R_2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkylaryl where aryl may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy;

R_1 and R_2 may together form a 5- or 6- membered ring which may contain 1 or 2 heteroatoms selected from N, O or S;

R_3 is halogen, CN, CF_3, SO_3CF_3, N_3, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, NH_2, NR_5R_6, COR_7, 5- or 6-membered

aryl which may contain 1 or 2 heteroatoms selected from N, O or S and being either (i) optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy or either (ii) fused at two adjacent carbon atoms to an aryl ring, said aryl ring being optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy;

R_4 is hydrogen or halogen;

R_5 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R_6 is C_1-C_6 alkyl or C_2-C_6 alkenyl; or

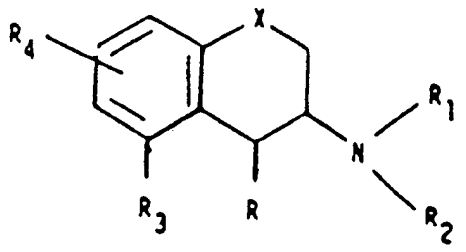
R_5 and R_6 may together form a 5- or 6- membered ring which may contain 1 or 2 heteroatoms selected from N, O or S;

R_7 is hydrogen, hydroxy, chloro, bromo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy; NR_8 R_9 or 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by one or more of halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy;

R_8 and R_9 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, or may together form a 5- or 6- membered ring containing 1 or 2 heteroatoms selected from N, O or S;

enantiomers or salts thereof.

A further aspect of the invention is a pharmaceutical preparation containing as active ingredient a compound according to formula I



I

wherein

X is O or $S(O)_p$;

p is an integer 0, 1 or 2;

R is hydrogen, fluoro or C_1-C_6 alkyl;

R_1 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R_2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkylaryl where aryl may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy; or

R_1 and R_2 may together form a 5- or 6- membered ring which may contain 1 or 2 heteroatoms

R_3 is halogen, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, NR_5R_6, COR_7, 5- or 6-membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S and being either (i) optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or

C_1-C_4 alkoxy or either (ii) fused at two adjacent carbon atoms to an aryl ring, said aryl ring being optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy;

R_4 is hydrogen or halogen;

R_5 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R_6 is C_1-C_6 alkyl or C_2-C_6 alkylen; or

R_5 and R_6 may together form a 5- or 6- membered ring which may contain 1 or 2 heteroatoms selected from N, O or S;

R_7 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, NR_8 R_9 or 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by one or more of halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy;

R_8 and R_9 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy or may together form a 5- or 6- membered ring containing 1 or 2 heteroatoms selected from N, O or S;

an enantiomer or a pharmaceutically acceptable salt thereof.

A preferred group of therapeutically active compounds of formula I are those wherein R_1 and R_2 are each independently hydrogen, n-propyl, i-propyl or cyclopropyl and R_3 is a carbonylgroup COR_7. Among these groups are the definition

of R_7 as alkyl, aminoalkyl e.g. methyl, ethyl, n-propyl, i-propyl, cyclopropyl, n-butyl, i-butyl, t-butyl and cyclobutyl or aryl, aminoaryl e.g. phenyl, thienyl, fluorophenyl and furanyl. Another preferred group is when R_3 is aryl e.g. phenyl, thienyl, furanyl, or fluorophenyl. Another preferred group is when R_3 is alkyl e.g. n-propyl, i-propyl or alkenyl e.g. i-propenyl and allyl. Another preferred group of active compounds are those wherein R_4 is halogen in 8 position as well as enantiomers thereof.

Compounds of formula I wherein R_3 is CN, COOH, COCl, COBr, NH_2, N_3, NO_2 or SO_3CF_3 are new intermediates for preparation of the therapeutically active compounds of formula I.

C_1-C_6 alkyl in formula I representing straight, branched and cyclic alkyl groups having 1 to 6 carbon atoms, for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl, i-hexyl, cyclopropyl, cyclobytyl, cyclopentyl, cyclohexyl, methylcyclopropyl, ethylcyclopropyl, methylcyclobutyl. Preferred alkyl groups have 1 to 4 carbon atoms.

C_2-C_6 alkenyl in formula I representing straight or branched carbon atoms chains having 2 to 6 carbon atoms and containing one or two double bond, for example allyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, isopentenyl. Preferred alkenyl groups have 2 to 4 carbon atoms and one double bond.

C_1-C_4 alkoxy in formula I representing a straight alkoxy group having 1 to 4 carbon atoms, for example methoxy, ethoxy, propoxy or butoxy, preferably methoxy and ethoxy.

C_1-C_4 alkylaryl where aryl may contain 1 or 2 heteroatoms selected from N, O or S in the definition of R_2 in formula I representing an aryl residue having 3 to 12 carbon atoms

in the aromatic ring and optionally 1 or 2 heteroatoms selected from N, O or S in the aromatic ring, bond by a straight or branched alkylen chain having 1 to 4 carbon atoms in the aliphatic chain. The aromatic ring may be substituted by one or more of nitrile, trifluoromethyl, halogen such as fluoro, chloro, bromo, iodo, C_1-C_6 alkyl, e.g. methyl, ethyl, propyl, C_2-C_6 alkenyl e.g. allyl, propenyl, or C_1-C_4 alkoxy preferably in meta and/or para position. Examples of suitable aryl groups in C_1-C_4 alkyl-aryl are phenyl, naphtyl, biphenyl, thienyl, furyl, pyryl, pyrimidyl and pyrridinyl. Preferred C_1-C_4 alkylaryl groups are unsubstituted and substituted phenylalkyl groups wherein the alkyl group is a straight or branched alkyl having 1 to 4 carbon atoms and the aromatic ring may be substituted by one or more of fluoro, chloro, bromo, iodo, nitrile, trifluoromethyl, methyl or ethyl in meta and/or para position. For example benzyl, phenethyl and phenyl-propyl, especially preferred is phenylpropyl.

Halogen in formula I representing fluoro, chloro, bromo, iodo, preferably fluoro, chloro and bromo.

5- or 6-membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S and being either (i) optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy or either (ii) fused at two adjacent carbon atoms to an aryl ring, said aryl ring being optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy; in the definition of R_3 in formula I representing either (i) substituted or unsubstituted phenyl, thienyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyradazinyl, thiozolyl, isothiozolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, piperazinyl or morpholinyl or either (ii) substituted or unsubstituted quinolyl, isoquinolyl, quinazolyl, quinaxazolyl or indolyl.

5- or 6-membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S in the definition of R_7, R_8 and R_9 in formula I representing phenyl, thienyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, piperazinyl, morpholinyl.

Examples of suitable 5- or 6-membered ring structures formed by R_1 and R_2 or R_5 and R_6, or R_7 and R_8 respectively and the nitrogen atom and which may contain a further heteroatom selected from N, O or S are piperazine, morpholine, pyrrolidine, pyrrole, pyrroline, imidazole, imidazoline, imidazolidine, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine.

The compounds of the invention have one or two assymetric carbon atoms. When R is hydrogen the compounds have an assymetric carbon atom adjacent to the nitrogen atom i.e. C_3 and when R is C_1-C_6 alkyl the compounds have an assymetric carbon atom adjacent to the nitrogen atom and an assymetric carbon atom adjacent to the alkyl group i.e. C_4. Thus, the compounds exist as two or four optical isomers i.e. enantiomers. Both the pure enantiomers, racemic mixtures are within the scope of the present invention. The therapeutic properties of the compounds may to a greater or lesser degree be ascribed to the racemate or to the enantiomers occurring.

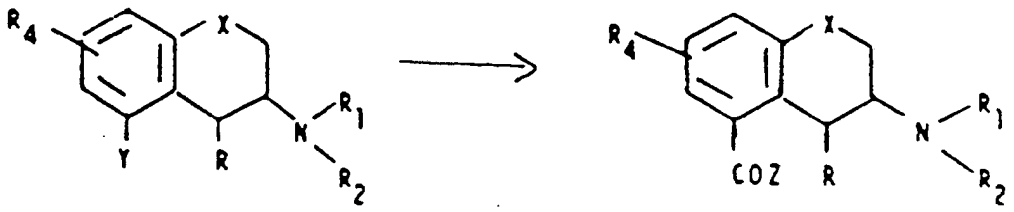
Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, oxalic, hydrochloric, formic, hydrobromic, citric, acetic, lactic, tartaric, pamoic, ethanedisulfonic, sulfamic, succinic, methylsulphonic, propionic, glycollic, malic, gluconic, pyruvic, phenyl-acetic, 4-aminobenzoic, anthranilic, salicylic, 4-amino-

salicylic, 4-hydroxybenzoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, naphtalenesulfonic, ascorbinic, cyclohexylsulfamic, fumaric, maleic and benzoic acids. These salts are readily prepared by methods known in the art.

Methods of Preparation

The compounds of the formula I may be prepared by the following processes constituting a further aspect of the invention.

a. Converting a compound of formula II

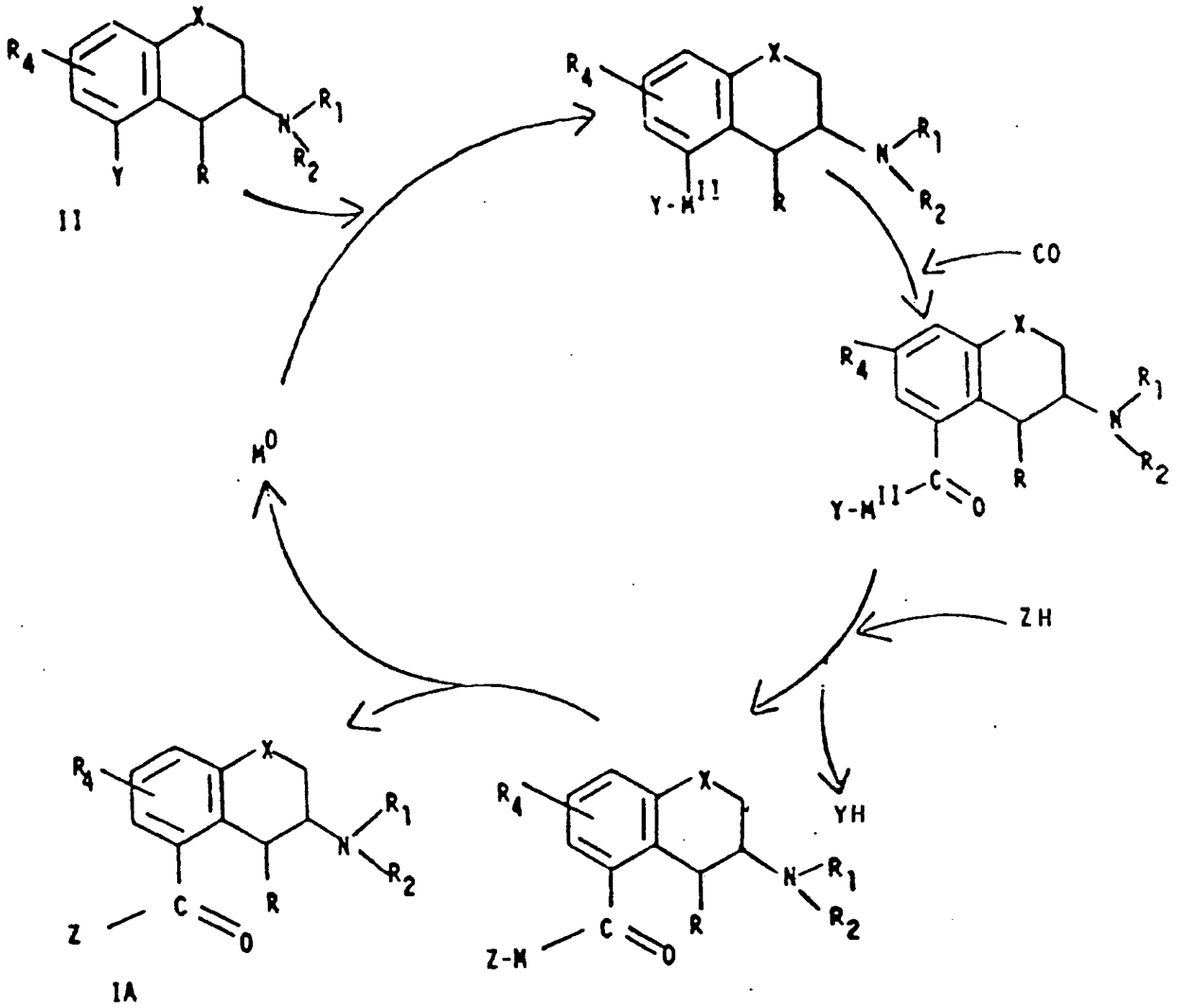


II IA

wherein Y is a leaving group such as trifluoromethane sulfonate (OSO_2CF_3), halide e.g. Cl or Br, and X, R, R_1, R_2 and R_4 are defined as above by substitution of the group Y to a carboxy group COZ, wherein Z is Cl, Br, OH, OR_p where R_p is C_1-C_6 alkyl to formation of a compound of formula I wherein R_3 is COZ, (IA).

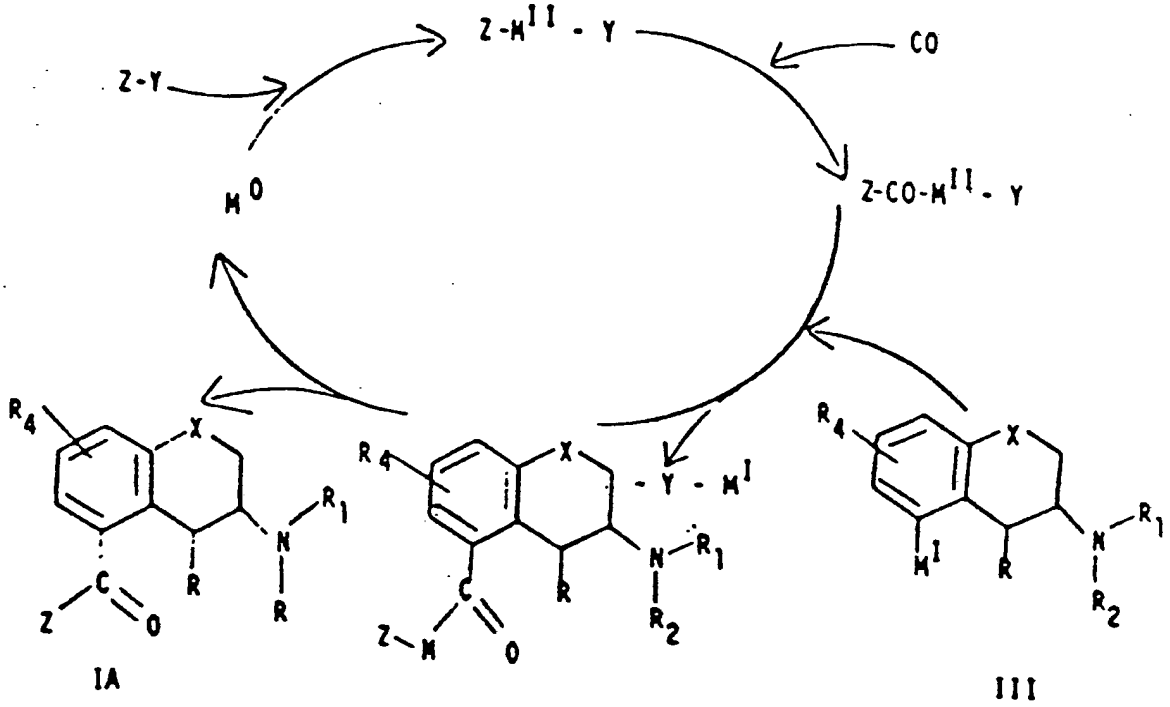
The compound of formula II can be converted to the compound of formula IA by the following catalytic cycle. Metal M^o should be a zerovalent transition metal, such as Pd or Ni with ability to undergo oxidative addition to aryl-Y-bonds e.g. the aryl-SO_3CF_3 bonds. M^o may be generated in situ

from M^{II}. The aryl-CO-M^{II}-Y are formed by treatment with carbon monoxide (CO).



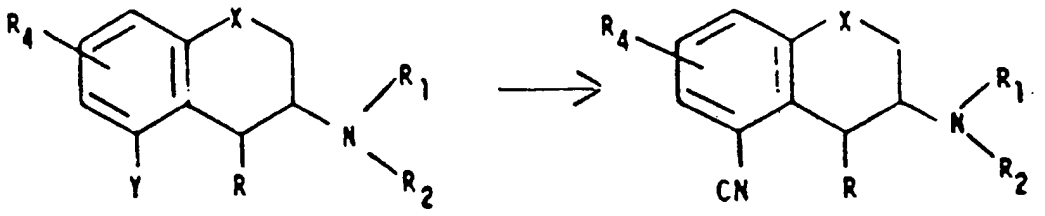
Further reagants are an alcohol such as alkanol e.g. methanol, ethanol, an amine base such as a trialkylamine e.g. triethylamine in an inert organic solvent preferentially a polar aprotic solvent such as dimethylformamide (DMF), dimethylsulfoxide (DMSO), aceton, acetonitrile etc. The reaction is normally performed at a temperature between +40 to + 120°C and at a pressure between 100 to 500 KPa. Optionally followed by hydrolyze and treatment with a thionyl halide e.g. thionylchloride to obtain the corresponding acid halide derivative.

b. Compound of formula I wherein R_3 is COZ (IA) can also be formed by the reversed process:
A reaction as the catalytic cycle using a zerovalent transition metal M^0, such as Pd, or Ni with ability to undergo an oxidation addition to Z-Y, wherein Z is defined Cl, Br, OH or OR_p where R_p is C_1-C_6 alkyl and Y is a leaving group such as SO_3CF_3 and halide, treatment with carbon monoxide followed by addition of a compound of formula III, wherein X, R, R_1, R_2 and R_4 are as defined under formula I.



The Z-CO-M^{II}-Y can also be formed from Z-COCl directly. The reaction conditions and reagant are the same as described in method a. above. Hydrolyze of suitable carboxylic acid ester forms the free acid, which can be converted to its acid halide derivative.

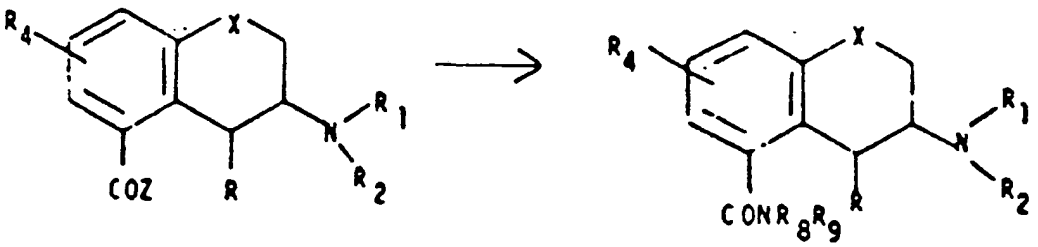
c. Converting a compound of formula II



II IB

wherein X, R, R_1, R_2 and R_4 are as defined above and Y is a leaving group such as Cl, Br or SO_3CF_3 by treatment with a cyanide reagant such as cupper cyanide (CuCN) to obtain a compound of formula I wherein R_3 is CN. The reaction with cyanide reagant is performed in an inert organic solvent such as dimethylformamide, hexamethylenphosphotriamide etc. at a temperature between 20° to 200°C preferrably between 50° to 150°C and at normal temperature.

d. Amination of a compound of formula IA



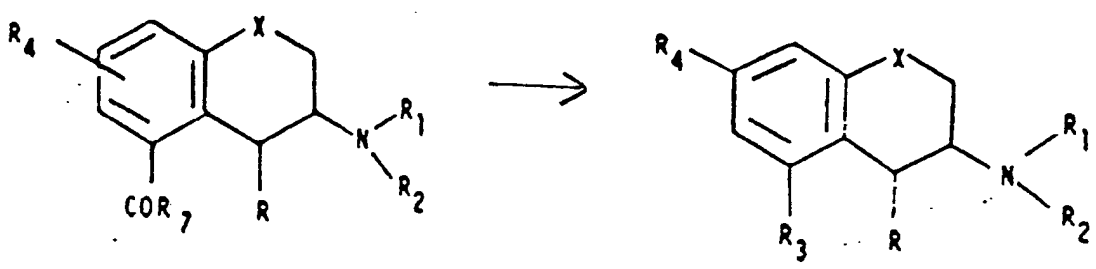
IA IC

wherein X, R, R_1, R_2 and R_4 are as defined above and Z is Cl, Br, OH or OR_p where R_p is C_1-C_6 alkyl.

If the compound of formula IA is a carboxylic acid ester it must first be hydrolyzed to form the free acid. The free acid is then transformed into the amide IC via its

acid chloride derivative by reaction of the corresponding amine NR_8R_9, where R_8 and R_9 are as defined under formula I, in a nonpolar aprotic solvent e.g. toluene, benzen at reflux temperature between 0 to 100°C.

e. Wittig reaction to formation of a compound of formula I where R_3 is a C_2-C_6 alkenyl group (IE),



ID IE

A 5-carboxy chroman/thiochroman derivative, where X, R, R_1, R_2 and R_4 are defined as above and R_7 is alkyl defined as above (ID) is converted by using a dipolar reagant such as alkyltriphenylphosphonium halide to formation of a corresponding alkenyl group (IE).

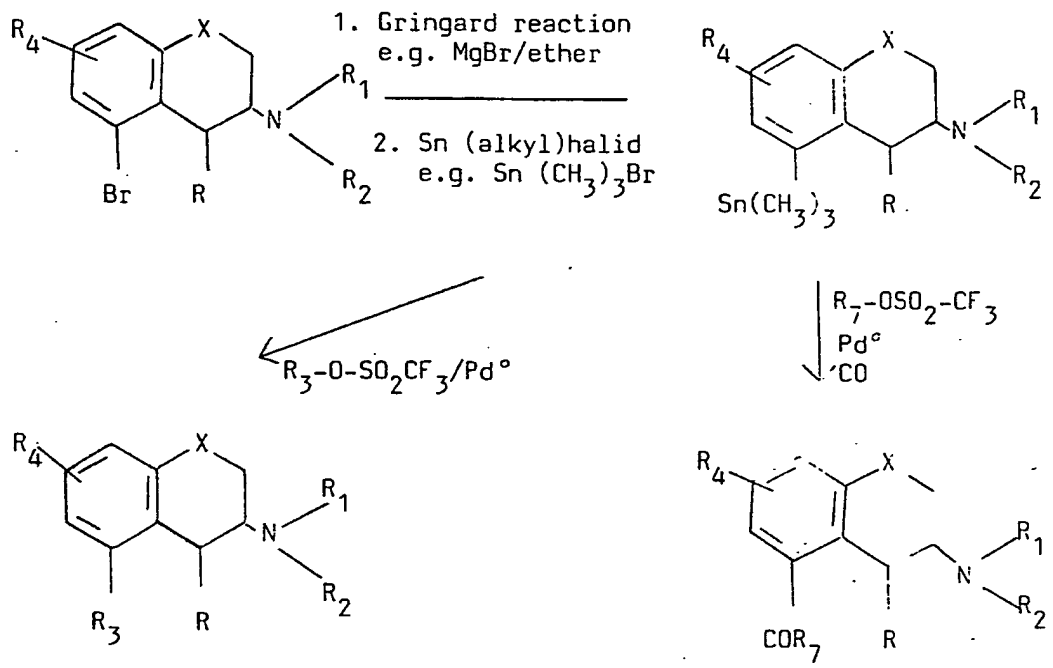
f. Catalytic hydrogenation of a 5-alkene chroman/thiochroman derivative of formula I wherein R_3 is a C_2-C_6 alkenyl group by using H_2/Pd, H_2/Pt or H_2/Raney Ni to formation of corresponding chroman/thiochroman derivative of formula I wherein R_3 is C_1-C_6 alkyl (IF).

g. Substitution of a 5-bromo-chroman/thiochroman derivative by treatment with an appropriate stannic trialkyl reagant in presence of a zerovalent metal preferrably palladium (Pd^o) to obtain a compound of formula I wherein R_3 is C_1-C_6 alkyl, C_1-C_4 alkenyl or aryl, in presence of carbonmonoxide (CO) is formed a compound of formula I

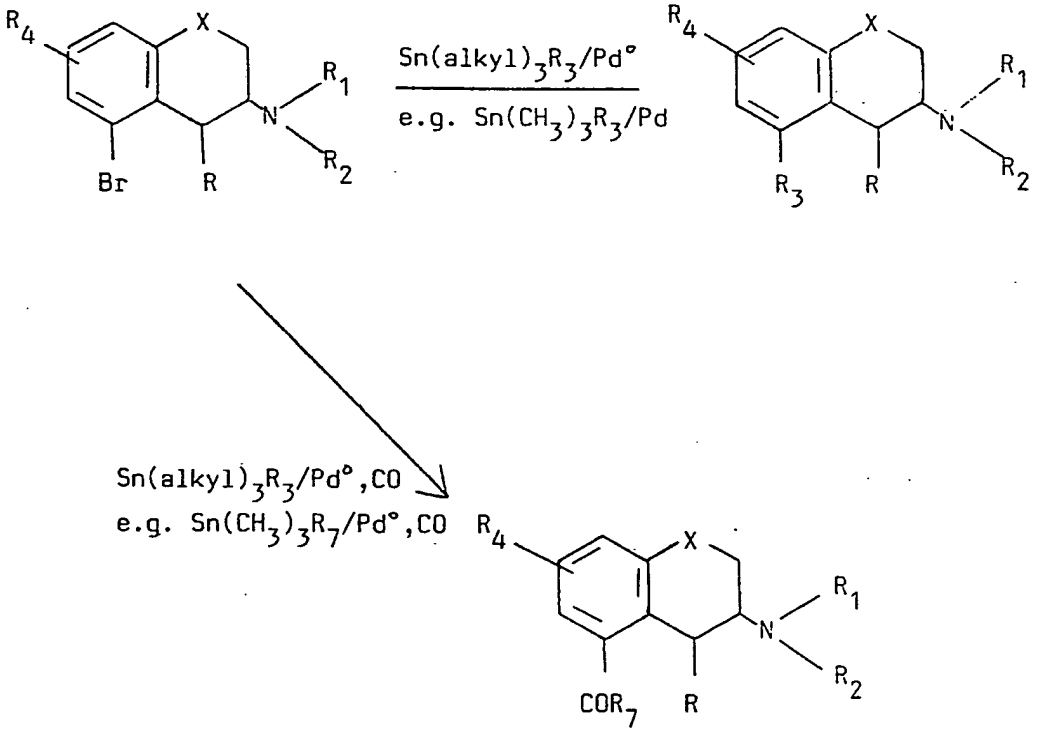
wherein R_3 is COR_7 wherein R_7 is C_1-C_6 alkyl, C_2-C_6 alkylen or aryl.

The substitution may be performed by one of the following ways:

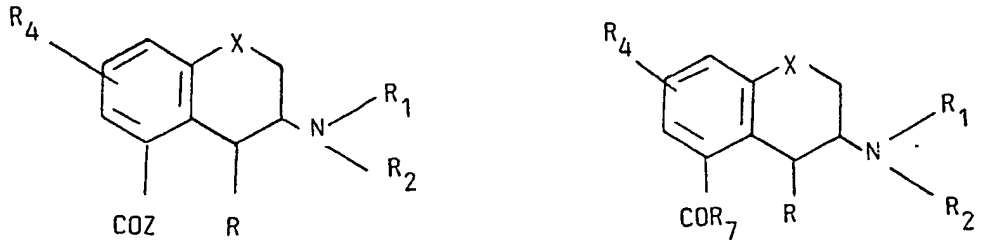
1)


1. Gringard reaction
e.g. MgBr/ether
2. Sn (alkyl)halid
e.g. Sn $(CH_3)_3Br$
R_3-O-SO_2CF_3/Pd°
R_7-OSO_2-CF_3
Pd°
CO

2)

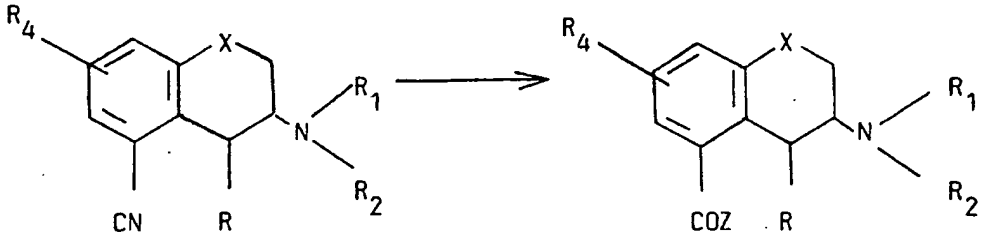

$Sn(alkyl)_3R_3$/Pd°
e.g. $Sn(CH_3)_3R_3$/Pd
$Sn(alkyl)_3R_3$/Pd°,CO
e.g. $Sn(CH_3)_3R_7$/Pd°,CO

h. Converting the 5-carboxy chroman/thiochroman derivative of formula I



where X, R, R_1, R_2 and R_4 are defined as above and Z is Cl, Br by using R_7Li wherein R_7 is alkyl, alkenyl or aryl as a cuprate reagant to obtain corresponding 5-keto-chroman/thiochroman derivative. Suitable R_7Li used is alkyllithium e.g. CH_3Li, alkenyllithium e.g. CH_2CHLi or aryllithium e.g. phenyl-Li. The reaction is performed in an inert organic solvent preferrably a nonpolar aprotic solvent such as ethers e.g. diethyl ether, tetrahydrofuran at a temperature between -50° - +50°C.

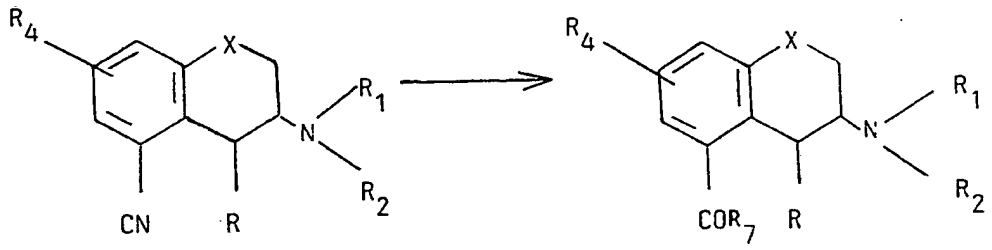
i. Hydrolysis of a compound of formula I, wherein R_3 is CN (IB)



IB IA

wherein X, R, R_1, R_2 and R_4 are as defined above optionally followed by treatment with a thionyl halide e.g. thionyl-chloride, thionylbromide to obtain a compound of formula I wherein R_3 is COZ where Z is OH, Cl or Br.

j. Substitution of a compound of formula I, wherein R_3 is CN (IB)

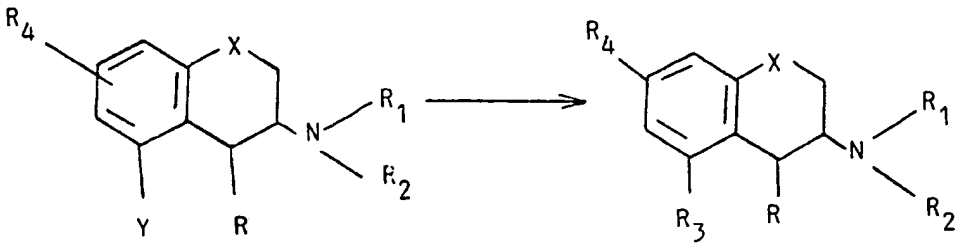


IB ID

wherein X, R, R_1, R_2 and R_4 are defined as above by treatment with an appropriate organometallic reagant preferentially an organolithium such as R_7Li or a Gringard reagent such as R_7Mg halide in an inert organic solvent preferentially a nonpolar aprotic solvent such as bensen, ethers e.g. diethylether, tetrahydrofuran followed by hydrolysis of the intermediate complex to obtain a compound of formula I wherein R_3 is COR_7 where R_7 is C_1-C_6 alkyl, C_2-C_6 alkenyl or aryl.

k. Hydrogeneration of a 5-alkene thiochroman/chroman derivative of formula I wherein R_3 is a C_2-C_6 alkenyl group by using H_2/Pd, H_2/Pt or H_2/Raney Ni or potassium azodicarboxylate to formation of corresponding thiochroman/chroman derivative of formula I wherein R_3 is C_1-C_6 alkyl.

l. Converting a compound of the formula (II)

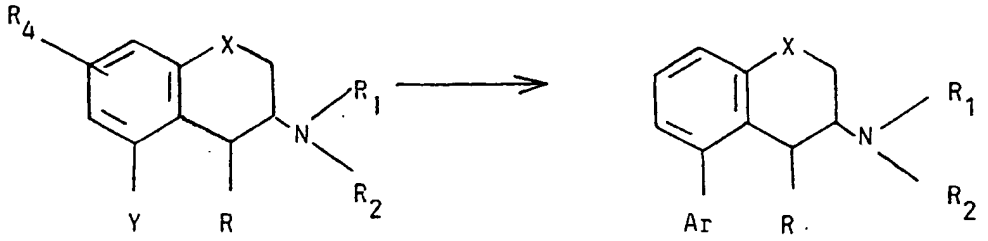


(II) (IE)

wherein Y is a leaving group such as trifluoromethanesulphonate (Tf), phosphonate, halide such as Br or J and R, R_1 and R_2 are defined as above by substitution of the group Y to R_3 where R_3 is a C_2-C_6 alkenyl group (IE).

The compound (II) may be converted to (IE) by reaction with a transition metal, such as Pd or Ni with ability to form ligand complex and undergo oxidative addition. A suitable alkenyl-substituent can be introduced via a suitable trialkylalkenylstannane.
Further reagents are an amine such as triethylamine and lithiumsalt e.g. lithium chloride. The reaction is preferentially carried out in a polar aprotic solvent such as dimethylformamide, dioxane, acetonitril or dimethylsulfoxide at a temperature between +40 to +120°C.

m. Converting a compound of the formula (II)

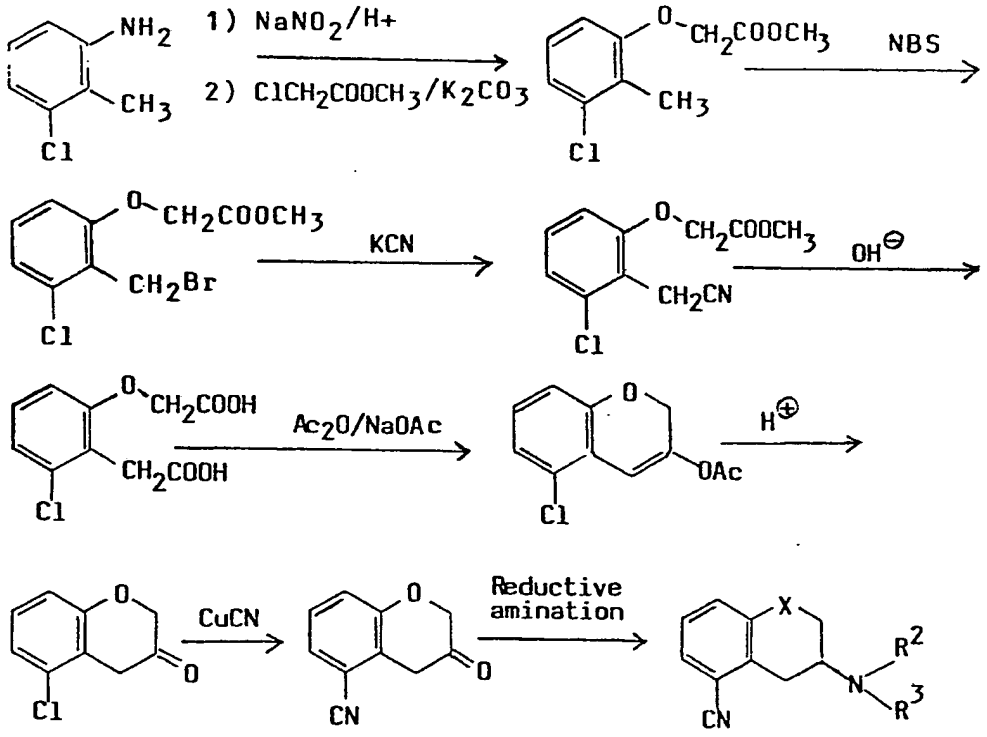


(II) (IF)

wherein Y is a leaving group such as trifluoromethanesulphonate (Tf), phosphonate, halide such as Br or J and R, R_1 and R_2 are defined as above by substitution of the group Y to 5- or 6-membered aryl (Ar) which may contain 1 or 2 heteroatoms selected from N, O, or S being either substituted or fused at two adjacent carbon atoms to an aryl ring as defined above to formation of a compound of formula IF.

The compound (II) may be converted to (IF) by reaction with a transition metal, such as Pd or Ni with ability to form ligand complex and undergo oxidative addition. A suitable aryl-substituent can be introduced via a suitable trialkylarylstannane or aryl-boric acid reagents.
Further reagents are an amine such as triethylamine and lithiumsalt e.g. lithium chloride. The reaction is preferentially carried out in a polar aprotic solvent such as dimethylformamide, dioxane, acetonitril or dimethylsulfoxide at a temperature between +40 to +120°C.

The following method describes one way of obtaining the intermediate of formula IB



wherein R_1, R^2 and R^4 are defined as in formula I

Pharmaceutical preparations

According to the present invention the compounds of the formula I will normally be administered orally, rectally or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or a pharmaceutically acceptable non-toxic acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, phosphate, sulphate, sulphamate, citrate, tartrate, oxalate and the like in a pharmaceutically acceptable dosage form. The dosage form may be a solid, semisolid or liquid preparation. Usually the active substance will constitute between 0.1 and 99% by weight of the preparation, more specifically between 0.5 and 20% by weight for preparations intended for injection and between 0.2 and 50% by weight for preparations suitable for oral administration.

To produce pharmaceutical preparations containing a compound of the formula I in the form of dosage units for oral application, the selected compound may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the table can be coated with a polymer known to the man skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compounds.

For the preparation of soft gelatine capsules, the active substance may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the active substance using either the abovementioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.2% to about 20% by weight of the active substance herein described, the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl-cellulose as a thickening agent or other excipients known to the man in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance, preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.01-100 mg/kg

bodyweight at peroral administration and 0.001-100 mg/kg bodyweight at parenteral administration.

Working examples

The following examples will further illustrate the invention.

Example 1

3-Dipropylamino-5-trifluoromethanesulfonylchroman

3-Dipropylamino-5-hydroxychroman (Thorberg et al. Acta Pharm. Suec. 24(1987)) (1.4 g, 4.0 mmol) and N,N-dimethylaminopyridine (0.1 g, 0.75 mmol) were dissolved in 50 mL methylene dichloride (CH_2Cl_2) and cooled to -30°C. 2,4,6-Collidine (0.75 mL, 5.7 mmol) was added followed by trifluoromethane sulfonic anhydride (1.0 mL, 6.0 mmol). The solution was stirred at -20°C for 3 hours and then allowed to reach ambient temperature. The solution was washed with aqueous $NaHCO_3$, dried with Na_2SO_4 and evaporated to dryness. The pale yellow oil was finally purified by flash chromatography (silica gel) by elution with ethyl acetate/hexane 1:9. Yield: 55%, Mp 125-127°C (oxalate).

Example 2

3-Dipropylamino-5-methyloxycarbonylchroman

3-Dipropylamino-5-trifluoromethanesulfonylchroman (Example 1; 4.43 g, 11.6 mmol) was dissolved in 80 mL dimethylformamide/methanol 6:2 and the solution was degassed (10 mm Hg, 20°C, 15 min). $PdOAc_2$ (76 mg, 0.34 mmol), 1,3-bis-diphenylphosphinopropane (141 mg, 0.34 mmol) and triethylamine (3.5 mL, 25 mmol) were then added. The mixture was heated to 70°C under CO atmosphere and stirred for 5 hours. The solution was cooled, diluted with toluene (200 mL), washed with aqueous $NaHCO_3$, dried with Na_2SO_4 and evaporated to dryness. The oil was purified by flash chromatography (silica gel) by elution with ethyl acetate/hexane 1:8.

Yield: 76%, Mp 150-152°C (HCl-salt).

Example 3

3-Dipropylamino-5-carbamoylchroman

3-Dipropylamino-5-methyloxychroman (Example 2; 400 mg, 1.37 mmol) was dissolved in 10 ml methanol and NaOH (60 mg, 1.5 mmol) in 2 mL H_2O was added. The mixture was refluxed for 5 hours, cooled, filtered through Celite" and evaporated to dryness. The residue was refluxed in $SOCl_2$ (5 mL, 68 mmol) for 30 minutes. The excess $SOCl_2$ was then removed in vacuo to give 3-dipropylamino-5-chloroformylchroman*HCL as a gum. The pale brown gum was dissolved in CH_2Cl_2 (50 mL), and a stream of NH_3 (g) was introduced during 2 minutes. The solution was washed with aqueous $NaHCO_3$, dried with Na_2SO_4 and evaporated to dryness. The oil was purified by flash chromatography (silica gel) by elution with ethyl acetate-/hexane 1:4. Yield 80%, ^{13}C-NMR: 172.0 154.9 136.5 126.9 120.4 119.1 118.6 67.8 53.0 52.6 26.1 22.4 21.9 14.1 11.7.

Example 4

3-dipropylamino-5-N,N-dimethylcarbamoylchroman

The title compound was prepared analogous to the procedure used in Example 3 starting from 3-dipropylamino-5-methyl-oxycarbonylchroman and substituting dimethylamine (g) in place of NH_3 (g). ^{13}C-NMR: 189.3 170.3 149.9 137.4 126.7 126.1 124.9 65.8 64.7 48.2 47.7 30.7 26.0 15.1 10.9.

Example 5

3-Dipropylamino-5-N,N-diisopropylcarbamoylchroman

The title compound was prepared analogous to the procedure used in Example 3 starting from 3-dipropylamino-5-methyloxy-chroman. Mp 228-230°C (HCl-salt).

Example 6
3-Dipropylamino-5-N-methylcarbamoylchroman

The title compound was prepared analogous to the procedure used in Example 3 starting from 3-dipropylamino-5-methyloxycarbonylchroman and substituting methylamine (g) in place of NH_3 (g). Mp 95-97°C (oxalate).

Example 7
3-Dipropylamino-5-acetylchroman

3-Dipropylamino-5-chloroformylchroman*HCl (4.42 g, 13.4 mmol), prepared from 3-dipropylamino-5-methyloxycarbonylchroman (Example 2) analogous to the procedure used in Example 3, in dry tetrahydrofuran (20 ml), was added to a pre-formed solution of lithium dimethylcuprate; prepared from MeLi and CuI, in 200 mL tetrahydrofuran at -78°C. The solution was stirred for 15 minutes at -78°C and was then allowed to reach room temperature during 10 minutes. Then, 30 mL H_2O was slowly added. The organic phase was decanted, dried with Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (silica gel) by elution with ethyl acetate/hexane 1:8. The title compound was crystallized as salt from ethyl acetate. Mp 106-108°C (oxalate).

Example 8
3-Dipropylamino-5-cyclopropylcarbonylchroman

The title compound was prepared analogous to the procedure used in Example 7 substituting lithium dicyclopropylcuprate (J. Org. Chem., 41 (22), 1976) in place of lithium dimethylcuprate. Mp 100-102°C (oxalate).

Example 9
3-Dipropylamino-5-tertbutylcarbonylchroman

The title compound was prepared analogous to the procedure used in Example 7 substituting lithium di-tertbutylcuprate (from tertbutyllithium and CuBr*Me_2S) in place of lithium dimethylcuprate. Mp 118-120°C (oxalate).

Example 10

3-Dipropylamino-5-isopropylcarbonylchroman

The title compond was prepared analogous to the procedure used in Example 7 substituting magnesium diisopropylcuprate (from isopropylmagnesium chloride and CuBr*Me_2S) in place of lithium dimethylcuprate. Mp 60-62°C (oxalate).

Example 11

3-Dipropylamino-5-(4-fluorophenylcarbonyl)chroman

The title compound was prepared analogous to the procedure in Example 7, substituting magnesiumdi(4-fluorophenyl)cuprate (from 4-fluorophenyl magnesium bromide and CuI) in place of lithium dimethylcuprate. Mp 98.3-98.4°C (oxalate).

Example 12

3-Dipropylamino-5-(2-thienylcarbonyl)chroman

The title compound was prepared analogous to the procedure used in Example 7 substituting lithium di(2-thienyl)cuprate (from 2-thienyllithium and CuI) in place of lithium dimethyl-cuprate. Mp 87-88.5 (oxalate).

Example 13

3-Dipropylamino-5-isopropenylchroman

Methyltriphenylphosphoniumbromide (0.62 g, 1.74 mmol) was dissolved in dry ethyl ether (20 ml) under nitrogen at ambient temperature and n-BuLi (0.7 ml, 2.5 M, 1.74 mmol) was added and the solution was stirred for 4 hours. 3-Dipropylamino-5-acetylchroman (Example 7; 0.40 g, 1.45

mmol) was dissolved in dry diethyl ether (2.0 ml) and this solution was added to the previously formed Wittig-reagent. The mixture was stirred at ambient temperature overnight. The solution was diluted with toluene and washed with water. Drying of the organic phase with Na_2SO_4 and evaporation to dryness gave a solid, which was finally purified by flash chromatography by elution with ethyl acetate/hexane 1:4. The collected fractions were evaporated and gave the title compound as a colourless oil. ^{13}C-NMR: 11.82 21.94 24.28 26.69 52.79 53.64 67.70 115.03 115.13 118.73 120.07 126.83 144.88 145.27 154.03.

Example 14

3-Dipropylamino-5-aminochroman

3-Dipropylamino-5-methyloxycarbonylchroman (Example 2; 1.0 g, 3.4 mmol) was dissolved in methanol (20 ml). Sodium hydroxide (0.16 g, 4.1 mmol) in water (1.0 ml) was added and the solution was refluxed with nitrogen overnight. The solution was evaporated to dryness, toluene (20 ml) was added and again the solution was evaporated to dryness. The residue was dissolved in toluene 20 ml, diphenylphosphoryl azid (1.87 g, 6.8 mmol) was added and the solution was refluxed for 2 hours. Methanol (2.0 ml) was added and reflux was continued for 4 hours. The solution was cooled, washed with water and extracted with dilute HCl (aq.). The acidic water phase was neutralized NaOH (aq.) and extracted with toluene. The toluene-phase was dried with sodium sulphate and evaporated to dryness. The residue was dissolved in ethanol containing 10% NaOH (20 ml) and the solution was refluxed overnight. The solution was cooled and diluted with toluene. Washing with water, drying of the organic phase and evaporation to dryness afforded the title compound as an oil, which was converted to a dihydrochloride salt. Mp 173-174°C.

Example 15
3-Dipropylamino-5-nitrochroman

3-Dipropylamino-5-aminochroman (Example 14; 0.050 g, 0.20 mmol) was dissolved in a mixture of trifluoracetic acid (0.080 ml, 1.0 mmol) in water (5 ml). The clear solution was cooled to 0-4°C. Sodium nitrite (0.017 g, 2.5 mmol) in water (1.0 ml), was added dropwise with good stirring. The solution was stirred for 15 minutes and neutralized with calcium carbonate. A solution of sodium nitrite (0.50 g, 7.2 mmol) in water (1.0 ml) was added followed by a mixture of copper sulfate (0.10 g, 0.62 mmol) and copper (1) oxide in water (1.0 ml). The solution was stirred at 0°C for 20 minutes and then at ambient temperature for 2 hours. The solution was extracted with diethyl ether. The organic phase was dried with sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel by elution with ethyl acetate/hexane 1:9 to give the title compound. Mp 150-151°C (hydrochloride).

Example 16
3-Dipropylamino-5-azidochroman

3-Dipropylamino-5-aminochroman (Example 14; 0.050 g, 0.20 mmol) was diazotized according to the procedure of Example 15. After stirring for 15 minutes, sodium azide (0.026 g, 0.4 mmol) in water (1.0 ml) was added. After stirring at 5°C overninght the solution was worked-up and purified according to the procedure of Example 15 to give the title compound. Mp 167-168°C (oxalate).

Example 17
3-Dipropylamino-5-(pyrrol-1-yl)chroman

3-Dipropylamino-5-aminochroman (Example 14; 0.60 g, 2.42 mmol) was dissolved in acetic acid (10 ml) and 2,5-dimethoxy-tetrahydrofuran (0.40 g, 3.0 mmol) was added. The solution

was refluxed for 1 hour. The solution was neutralized with NaOH (aq.) and extracted with toluene. The organic phase was dried with sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel by elution with ethyl acetate/hexane 1:9 to give the title compound. ^{13}C-NMR: 111.75 21.89 24.81 52.69 53.15 67.94 108.93 115.67 118.22 118.44 121.87 127.22 141.47 155.27

Example 18

3-(Methyl(3-phenylpropyl)amino)-5-hydroxychroman

3-Amino-5-methoxychroman (Thorberg et al. Acta Pharm. Suec. 24(1987)) (2.0 g, 9.28 mmol) was dissolved in methanol (50 ml) and pH was adjusted to 6.0 with acetic acid. The solution was cooled to 0°C and sodium cyanoborohydrid (0.87 g, 13.8 mmol) was added together with 3-phenylpropanal (1.22 ml, 9.28 mmol), the cooling was withdrawn and the solution was stirred at ambient temperature for 4 hours. Paraformaldehyde (0.42 g, 14 mmol) and sodium cyanoborohydride (0.87 g, 9.28 mmol) was added and stirring was continued overnight at ambient temperature. The solution was diluted with toluene and washed with water. Drying with sodium sulfate and evaporation to dryness gives an oil. The oil was purified by flash chromatography on silica gel by elution with ethylacete/hexane 1:4. The collected fractions were evaporated to give an oil. The oil was treated with HBr (47% aq.) at 120°C for 1 hour. The solution was cooled and neutralised with sodium hydroxide and extracted with toluene. The organic phase was dried and evaporated to give the title compound as an oil. ^{13}C-NMR: 22.502 29.09 33.47 38.19 53.66 67.75 102.04 109.20 110.46 125.78 127.05 128.36 142.20 155.29 158.28.

Example 19

3-(methyl(3-phenylpropyl))amino-5-methyloxycarbonylchroman

3-(methyl(3-phenylpropyl))amino-5-hydroxychroman (Example

18; 1.0 g, 3.37 mmol) was dissolved in CH_2Cl_2 (20 ml) at -20°C. Pyridine (0.32 ml, 4 mmol), trifluoromethanesulfonic anhydride (0.65 ml, 5.9 mmol) and dimethylaminopyridine (DMAP), (0.041 g, 0.59 mmol) was added at -20°C under nitrogen. The solution was stirred for 3 hours at -20°C. Cooling was withdrawn and the solution was diluted with toluene, washed with sodium hydrogen carbonate (aq.), dried with sodium sulfate, filtered through silica gel and evaporated to dryness. The remaining oil was dissolved in 13 ml degassed methanol/DMF 3:10. Palladium acetate (0.056 g, 0.25 mmol), 1,3-bis(diphenylphosphino)propane (0.103 g, 0.25 mmol) and triethyl amine (0.76 ml, 5 mmol) was added and the solution was flushed with CO(g) under vigorous stirring. The pressure in the reaction vessel was raised to 20.2 KPa(e) with the aid of a CO(g)-cylinder fitted with a regulator. Stirring was continued overnight at 75°C. The pressure and temperature was normalized and the solution was diluted with toluene and washed with water. The organic phase was dried and evaporated to dryness. The remaining oil was purified by flash chromatography on silica gel by elution with ethyl acetate/hexane 1:4. The collected fractions were evaporated to give the title compound as a colourless oil. ^{13}C-NMR: 26.88 29.00 33.20 37.85 51.64 53.37 55.44 67.24 120.60 123.06 123.40 125.59 126.47 128.17 128.24 130.36 142.01 154.93 167.29.

Example 20

3-(methyl(3-phenylpropyl))amino-5-N-methylcarbamoyl chroman

3-(methyl(3-phenylpropyl))amino-5-methyloxycarbonylchroman (Example 19; 0.32 g, 0.94 mmol) was dissolved in methanol (10 ml). NaOH (0.08 g, 2 mmol) in 1 ml water was added and the solution was refluxed overnight under nitrogen. The solution was evaporated to dryness and co-evaporated with toluene (10 ml) to dryness again. The remaining solid was refluxed in $SOCl_2$ for 30 minutes and evaporated to dryness. The pale brown gum was dissolved in tetrahydrofuran (THF) 20

ml and treated with methyl amine (g) for 1 minute under vigorous stirring. The solution was diluted with toluene and washed with sodium hydrogencarbonate (aq.). Drying and evaporation gave a gum, which was finally purified by flash chromatography on silica gel by elution with ethyl acetate-/hexane 1:2. The collected fractions were evaporated to give the title compound as a colourless gum. Crystallization from ethyl acetate as oxalate gave white needles. Mp 150-151°C. (oxalate).

Example 21

3-Dipropylamino-5-trifluoromethanesulfonylthiochroman

3-Dipropylamino-5-hydroxybenzothiopyran (EP 0222 996; 420 mg, 1.58 mmol) and collidine (0.27 g, 0.29 mL) were dissolved in 15 mL of CH_2Cl_2 and cooled to -30°C. Trifluoromethanesulfonic anhydride (0.54 g, 0.32 mL) was added dropwise and allowed to reach ambient temperature, and after 20 minutes diluted with methylendichloride. The solution was washed with saturated $NaHCO_3$, dried with Na_2SO_4, and evaporated in vacuo. Chromatography on silica by elution with $CHCl_3$ gave 0.62 g of the title compound as the base. Yield: 98%. Mp. 37-8°C; ^{13}C NMR (200 MHz-$CDCl_3$) PPM 148.3, 136.7, 128.4, 127.2, 126.3, 122.0, 117.1, 115.2, 55.6, 52.5, 28.0, 26.6,-22.6,11.8.

Example 22

3-Dipropylamino-5-methyloxycarbonylthiochroman

3-Dipropylamino-5-hydroxybenzothiopyran (EP 0222 996; 620 mg, 1.6 mmol) was dissolved in 11 mL of dimethyl-formamide/methanol (6:2) and the solution was degassed (10 mm, 22°C, 15 min). $Pd(OAc)_2$ (11mg), 1,3-bis-diphenyl-phosphinopropane (19 mg), and triethylamine (0.48 mL, 0.35 g) were added to the reaction mixture.

The mixture was heated to 70°C under carbonmonoxide atmosphere and stirred for 5 hours.
The solution was cooled, diluted with 30 mL of toluene, washed with saturated $NaHCO_3$, dried with Na_2SO_4, and evaporated in vacuo.
Chromatography on silica by elution using a gradient $CHCl_3$ -> 10% EtOAc/$CHCl_3$ gave 310 mg of the title compound (base) as a slightly yellow oil; Yield: 64%. ^{13}C NMR (200 MHz-$CDCl_3$) PPM 168.2, 136.6, 134.8, 131.6, 130.1, 126.5, 125.7, 56.7, 52.5, 52.1, 30.4, 28.0, 22.3, 11.9.

Example 23
3-Dipropylamino-5-acetylthiochroman

3-Dipropylamino-5-methyloxycarbonylthiochroman (Example 22; 310 mg, 1.01 mmol) was dissolved in 8 mL methanol and 60 mg of sodium hydroxide in 2 mL water was added. After 5 hours reflux the mixture was cooled and evaporated in vacuo. The residue was dissolved in thionylchloride (5 ml) and refluxed for 1 hour. The excess thionylchloride was evaporated in vacuo to obtain a gum.
The residual gum was dissolved in a minimal amount of tetrahydrofuran and added dropwise to a cooled (-78°C) solution of lithium dimethyl cuprate (2.02 mmol) in 20 mL of tetrahydrofuran.
The reaction mixture was stirred for 15 minutes at -78°C, then allowed to reach ambient temperature and after 10 minutes the reaction was quenched with 0.9 mL of water.
The reaction was filtered through Celite" and evaporated to dryness.
The residue were dissolved in ether, washed with saturated $NaHCO_3$, treated with brine, dried with Na_2SO_4, and evaporated in vacuo to afford the crude base as an oil.
The crude residue was chromatographed on silica by elution using a gradient of $CHCl_3$ -> 5% EtOAc/$CHCl_3$.
The hydrochloride salt was obtained by dissolving the pure base in ether and dropping an excess of an ethereal HCl

solution. Recrystallization in trichloromethane/diethylether gave 92 mg of the title compound as a white solid; Yield: 27%. Mp 141-2°C; ^{13}C NMR (200 MHz-$CDCl_3$) PPM 201.9, 138.4, 135.9, 131.7, 131.2, 127.2, 127.0, 59.9, 54.1, 51.8, 29.9, 27.9, 26.1, 18.6, 18.2, 11.6.

Example 24
5-Allyl-3-(dipropylamino)thiochroman

To a solution of 3-(dipropylamino)-5-trifluoromethanesulfonylthiochroman (Example 21; 1.28 g, 3.22 mmol), tetrakis(triphenylphosphine)palladium(0) (76 mg, 0.064 mmol) and a few crystals of 2,6-di-t-butyl-4-methylphenol in 10 mL anhydrous toluene was 1.17 g (1.1 mL, 3.53 mmol) tributylallyltin added neat. The resulting solution was refluxed for 4 hours then pyridine (1 mL) was added to the cooled solution followed by 2.1 ml of a hydrogen fluoride-pyridine complex (Stille J.K. et al. JOC 52(1987) 422).
After stirring for 1 hour at room temperature, the reaction mixture was diluted with 50 ml dietyl ether and treated, successively, with 50 mL 1 M NaOH solution, H_2O (x2), washed with a saturated NaCl solution and dried ($NaSO_4$). After filtering and removal of the solvent in vacuo, the crude was obtained as a dark oil.
Chromatography on silica by elution using a gradient hexane -> 5% EtOAc/hexane gave 0.85 g of the title compound (base) as a slightly yellow oil. Yield: 91%. ^{13}C NMR: (200 MHz-$CDCl_3$) PPM 139.0, 136.5, 134.0, 133.0, 126.1, 125.9, 125.0, 116.0, 57.0, 52.6, 37.7, 29.5, 27.7, 22.5, 11.9.
A portion of the base was taken out and made into the hydrochloride salt by dissolving the pure base in ether and dropping an excess of an ethereal HCl solution. Recrystallizing (AcCN-Et20-hexane) gave a white solid. Mp 164-5°C.

Example 25
3-(Dipropylamine)-5-propylthiochroman hydrochloride

To a stirred suspension of potassium azodicarboxylate (0.76 g, 3.9 mmol) (made fresh from diethyl azocarboxylate and potassium hydroxide) and 5-allyl-3-(N,N-dipropylamino)-thiochroman (Example 24; 0.4 g, 1.4 mmol) in 10 mL anhydrous methanol was added a solution of glacial acetic acid/methanol (1:4) until the yellow color (from the potassium salt) disappeared.

After 30 min stirring at room temperature more potassium azodicarboxylate (200 mg) was added and again decomposed as before. This process was continued until analysis (GC) showed no starting material remaining.

Upon completion, (2 hours and 4 additions of the potassium salt) the solvent was removed in vacuo. To the remains, a 2 M NaOH solution was added which was extracted (x2) with diethyl ether and the combined organic portions were treated with a saturated NaCl solution, and dried (Na_2SO_4). The crude base was obtained as a light colored oil upon the removal of the solvent in vacuo.

Chromatography on silica by elution using a gradient hexane - 5% EtOAc/hexane gave the title compound (base) as a clear oil. The hydrochloride salt was made by dissolvning the pure base in ether and dropping and an excess of an ethereal HCl solution. Recrystallizing (chloroform-Et_2O) gave 0.30 g of a white solid. Yield: 66%. Mp 150-151°C. ^{13}C NMR: (on base, 200 MHz-$CDCl_3$) PPM 141.6 133.7 132.8, 125.8, 125.6, 124.5, 57.1, 52.6, 35.3, 29.5, 27.6, 23.6, 22.4, 14.3, 11.9.

Pharmacology

Pharmacological treatment of depression in man

Evidence is available that in depressed patients the neurotransmission in the central nervous system (CNS) may be disturbed. These disturbances appear to involve the neurotransmitters noradrenaline (NA) and 5-hydroxytryptamine (5-HT). The drugs most frequently used in the treatment of depression are considered to act by improving the neurotransmission of either or both of these physiological

agonists. Available data suggest that the enhancement of 5-HT neurotransmission will primarily improve the depressed mood and anxiety, whereas the enhancement of noradrenaline neurotransmission will rather improve the retardation symptoms occurring in depressed patients. In recent years many efforts have been made to develop new drugs with high selectivity for the improvement of the 5-HT neurotransmission in the CNS.

The mechanism of action for the drugs generally used today in the therapy of mental depression is indirect, i.e. they act by blocking the reuptake of the neurotransmitters (NA and/or 5-HT) released from nerve terminals in the CNS, thus increasing the concentration of these transmitters in the synaptic cleft and hence restoring an adequate neurotransmission.

A fundamentally different way to improve the neurotransmission in the central 5-HT-neurons would be to use a direct 5-HT-receptor agonist. In order to minimize side effects, a high selectivity for this kind of receptors would then be preferable.

Antagonisms of the inhibitory autoreceptors located on the cellbodies of 5-HT-neurons would be another fundamentally different way to improve the 5-HT neurotransmission.

Surprisingly, we have found that a group of compounds of the formula I have selective, direct stimulating or inhibitory effect on a subgroup of central 5-HT receptors. Another observation is that some of those compounds have a particularly good oral bioavailability. In order to evaluate the 5-HT-receptor stimulating effect and selectivity, the affinity for various receptors in rat brain were measured in vitro using receptor assays (Ki nM).

In vitro test: Receptor binding assay

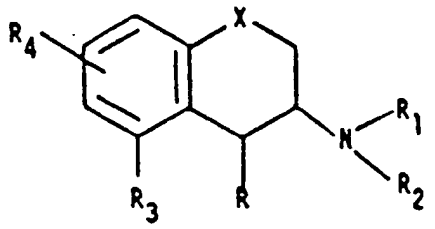
$5HT_{1A}$ binding assay. Cerebral cortex + hippocampus from each rat was dissected and homogenized in 15 ml ice-cold 50 mM Tris-HCl buffer 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5 with an Ultra-Turrax (Janke & Kunkel, Staufen, FRG) for ten s. After centrifugation for 12.5 min at 17,000 rpm (39,800 x g in a Beckman centrifuge with a chilled JA-17 rotor (Beckman, Palo Alto, CA, USA), the pellets were re-suspended in the same buffer and homogenization and centrifugation repeated. To each pellet 5 ml ice-cold 0.32 M sucrose were added and homogenized for 5 sec. These samples were kept frozen at -70°C. When used they were diluted with the buffer to 8 mg tissue/ml and homogenized for 10 sec. The tissue homogenates were incubated for ten minutes at 37°C and then supplied with 10 µM pargyline followed by reincubation for 10 minutes.

The binding assay followed that described by Peroutka, J. Neurochem. 47, 529-540, (1986). The incubation mixture (2 ml) contained ^{3}H-8-OH-DPAT (0.25 to 8 nM), 5 mg/ml tissue homogenate in 50 mM Tris-HCl buffer containing 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5. Six different concentrations of ^{3}H-8-OH-DPAT were analyzed. Binding experiments were started by the addition of tissue homogenate and followed by incubation at 37°C for 10 minutes. The incubation mixtures were filtered through Whatman GF/B glass filters with Brandel Cell Harvester (Gaithersburg, MD, USA). The filters were washed twice with 5 ml ice-cold 50mM Tris-HCl buffer, pH 7.5, and counted with 5 ml Ready-solv HP (Beckman) in a Beckman LS 3801 scintillation counter. Non-specific binding was measured by the addition of 10 µM 5-HT to the reaction mixture. The binding data was processed by non-linear least squares computer analysis (Munson and Rodbard, Anal. Biochem. 107, 220-239, (1980).

The test results are expressed as K_i and are given in nM. For instance, 3-dipropylamino-5-acetylchroman has K_i 1,0 (nM), 3-dipropylamino-5-carbamoylchroman has K_i 3,1 (nM), 3-dipropylamino-5-N-methylcarbamoylchroman has K_i 3,3 (nM) and 3-dipropylamino-5-(2-thienylcarbonylchroman has K_i 1,7 (nM).

Claims

1. A compound of the formula



(I)

wherein

X is O or $S(O)_p$;

p is an integer 0, 1 or 2;

R is hydrogen, fluoro or C_1-C_6 alkyl;

R_1 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R_2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkylaryl where aryl may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy; or

R_1 and R_2 may together form a 5- or 6- membered ring which may contain 1 or 2 heteroatoms selected from N, O or S;

R_3 is halogen, CN, CF_3, SO_3CF_3, N_3, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, NH_2, NR_5R_6, COR_7, 5- or 6-membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S and being either (i) optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl,

C_2-C_6 alkenyl or C_1-C_4 alkoxy or either (ii) fused at two adjacent carbon atoms to an aryl ring, said aryl ring being optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy;

R_4 is hydrogen, C_1-C_6 alkyl or halogen;

R_5 is hydrogen C_1-C_6 alkyl or C_2-C_6 alkenyl;

R_6 is C_1-C_6 alkyl or C_2-C_6 alkenyl; or

R_5 and R_6 may together form a 5- or 6-membered ring which may contain 1 or 2 heteroatoms selected from N, O or S;

R_7 is hydrogen, hydroxy, chloro, bromo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, NR_8 R_9 or 5- or 6-membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by one or more of halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_1-C_4 alkoxy;

R_8 and R_9 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy or may together form a 5- or 6- membered ring containing 1 or 2 heteroatoms selected from N, O or S;

an enantiomer or a salt thereof.

2. A compound according to claim 1 cherein X is O.

3. A compound according to claim 1 wherein

$(O)_p$
‖
X is S and p is 0, 1 or 2.

4. A compound according to claim 1 wherein

$(O)_p$
‖
X is S and p, R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are defined as in claim 1 with the proviso that when R is hydrogen or C_1 -C_6 alkyl then R_3 cannot be halogen or C_1 -C_6 alkyl.

5. A compound according to claim 1 wherein X is

$(O)_p$
‖
S and p is 0, R_1 and R_4 is hydrogen, R and R_2 are propyl with the proviso that R_3 cannot be propyl.

6. A compound according to any of claims 1, 2, 3, 4 or 5 wherein R_3 is halogen, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, NR_5 R_6, COR_7, 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S and being either (i) optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy or either (ii) fused at two adjacent carbon atoms to an aryl ring, said aryl ring being optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy; R_7 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, NR_8 R_9 or 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by one or more of halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_1-C_4 alkoxy; X, P, R, R_1, R_2, R_4, R_5, R_6, R_8 and R_9 are defined as in claim 1, an enantiomer or a pharmaceutically acceptable salt thereof for use in theraphy.

7. A compound according to any of claims 1-6, wherein R_1

and R_2 are the same or different and selected from hydrogen, n-propyl, i-propyl and cyclopropyl.

8. A compound according to any of claims 1-7 wherein R_3 is COR_7.

9. A compound according to claim 8 wherein R_7 is C_1-C_4 alkyl, phenyl, furanyl or thienyl optionally substituted with halogen, NR_8 R_9 wherein R_8 and R_9 are each independently hydrogen or C_1-C_4 alkyl, or C_1-C_4 alkoxy.

10. A compound according to claim 8 wherein R and R_4 are hydrogen, R_1 and R_2 are n-propyl and R_7 is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, n-butyl, i-butyl, t-butyl, cyclobutyl, thienyl, furanyl, phenyl, amino, N-methylamino, methoxy or fluorophenyl.

11. A compound according to any of claims 1-7 wherein R_3 is phenyl, furanyl, thienyl or fluorophenyl.

12. A compound according to any of claims 1-7 wherein R_3 is n-propyl, i-propyl, i-propenyl or allyl.

13. A compound according to any of claims 1-9, 11-12 wherein R_4 is halogen in 8 position.

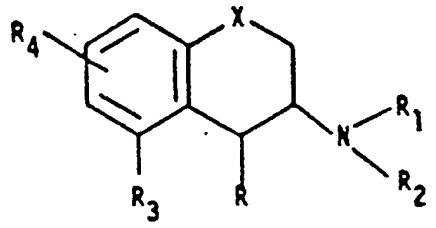
14. A compound according to claim 1 which is
3-dipropylamino-5-acetylchroman,
3-dipropylamino-5-carbamoylchroman,
3-dipropylamino-5-N-methylcarbamoylchroman and
3-dipropylamino-5-(2-thienylcarbonyl)chroman.

15. A compound according to claim 1 wherein R_3 is CN, COOH, COCl, COBr, Br, N_3, NO_2, SO_3CF_3 or NH_2, and X, R, R_1, R_2 and R_4, are as defined in claim 1, an enantiomer or a salt thereof.

16. A compound according to claim 15 wherein R_1 and R_2 are the same or different and selected from hydrogen, n-propyl, i-propyl and cyclopropyl.

17. A compound according to claim 16 wherein R and R_4 are hydrogen, R_1 and R_2 are n-propyl and R_3 is SO_3CF_3.

18. A pharmaceutical preparation containing as active ingredient a compound according to formula I



I

wherein

X is O or $\overset{(O)_p}{\overset{\|}{S}}$;

p is an integer 0, 1 or 2;

R is hydrogen, fluoro or C_1-C_6 alkyl;

R_1 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl;

R_2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkylaryl where aryl may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy; or

R_1 and R_2 may together form a 5- or 6- membered

ring which may contain 1 or 2 heteroatoms selected from N, O or S;

R_3 is halogen, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, NR_5 R_6, COR_7, 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S and being either (i) optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy or either (ii) fused at two adjacent carbon atoms to an aryl ring, said aryl ring being optionally substituted by one or more substituents independently selected from halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_1-C_4 alkoxy;

R_4 is hydrogen alkyl or halogen;

R_5 is hydrogen, C_1-C_6 alkyl or C_2-C_6 alkylen;

R_6 is C_1-C_6 alkyl or C_2-C_6 alkylen; or

R_5 and R_6 may together form a 5- or 6- membered ring which may contain 1 or 2 heteroatoms selected from N, O or S;

R_7 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, NR_8 R_9 or 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by one or more of halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_1-C_4 alkoxy;

R_8 and R_9 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, 5- or 6- membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S optionally substituted by halogen, CN, CF_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy or may

together form a 5- or 6-membered ring containing 1 or 2 heteroatoms selected from N, O or S;

an enantiomer or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical preparation according to claim 18 wherein R, R_1, R_2, R_3, R_4, R_7, R_8 and R_9 are defined as in any of claims 7-14.

20. A compound according to any of claims 6-14 for use in the treatment of disorders in the centralnervous system, especially 5-hydroxy tryptamine medicated disorders.

21. A compound according to claim 20 for use in the treatment of depression, anxiety, anorexia, senile dementia, migraine, Alzheimer's disease, hypertension, termoregulator and sexual disturbances, pain and disturbances in the cardiovascular system.

22. Use of a compound according to any of claims 6-14 for the manufacture of a medicament for treatment of disorders in the central nervous system, especially 5-hydroxy tryptamine medicated disorders.

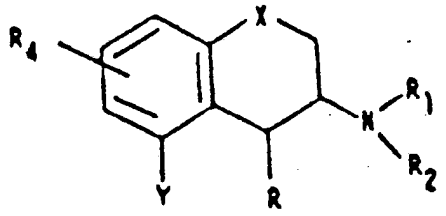
23. Use according to claim 22 for the manufacture of a medicament for treatment of depression, anxiety, anorexia, senile dementia, migraine, Alzheimer's disease, termoregulator and sexual disturbances, pain and disturbances in the cardiovascular system.

24. A method for treatment of disorders in the central nervous system, especially 5-hydroxytryptamine mediated disorders by administering to mammals and man a compound defined in any of claims 6-14, an enantiomer or a physiologically acceptable salt thereof.

25. A method according to claim 24 for treatment of depression, anxiety, anorexia, senile dementia, migraine, Alzheimer's disease, termoregulator and sexual disturbances, pain and disturbances in the cardiovascular system.

26. A process for the preparation of a compound of the formula I according to any of claims 1-17, by

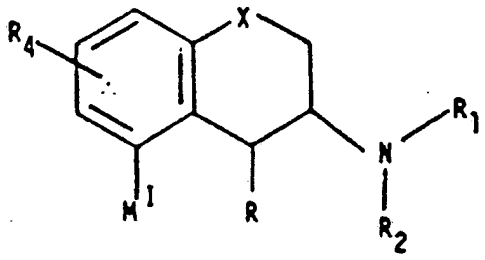
a) converting a compound of formula II



II

wherein Y is a leaving group and X, R, R_1, R_2 and R_4 are as defined under formula I by a catalytic cycle using a zerovalent transition metal (M), which undergoes an oxidative addition to the aryl-Y-bonds, treatment with carbon monoxide followed by Z-H , where Z is Cl, Br, OH, OR_p, where R_p is C_1-C_6 alkyl, and the initially formed carbonylated σ-aryl-metal-Y complex, to formation of a compound of formula I wherein R_3 is COZ (IA).

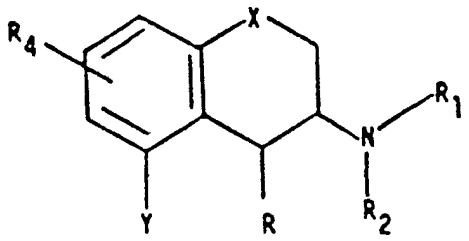
b) reaction by a catalytic cycle using a zerovalent transition metal (M^o) which undergoes an oxidative addition to Z-Y, wherein Z is defined Cl, Br, OH, OR_p, where R_p is C_1-C_6 alkyl and Y is a leaving group, treatment with carbon monoxide, followed by addition of the compound of the formula III



III

wherein X, R, R_1, R_2 and R_4 are as defined under formula I and M^I is a transition metal to formation of a compound of formula I wherein R_3 is COZ (IA).

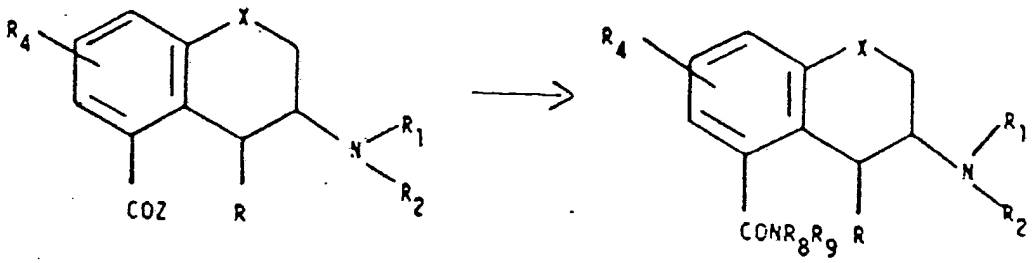
c) converting a compound of formula II



II

wherein X, R, R_1, R_2 and R_4 are as defined under formula I and Y is a leaving group such as SO_3CF_3, halide by treatment with a cyanide reagent, to formation of a compound of formula I wherein R_3 is CN (IB).

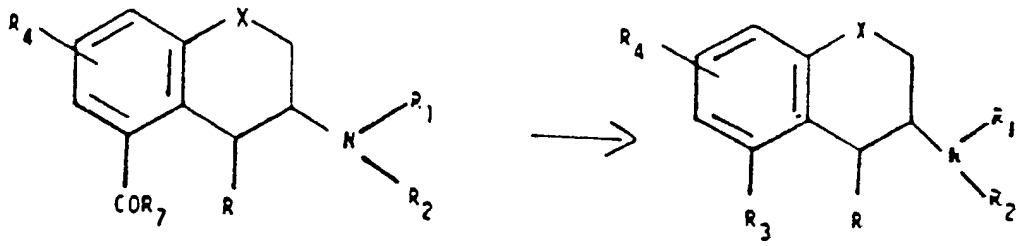
d. amination of a compound of formula IA



IA IC

wherein X, R, R_1, R_2, and R_4, are as defined under formula I and Z is Cl, OH or OR_p, where R_p is C_1-C_6 alkyl by reaction with NHR_8R_9 to give the corresponding amide of formula I, where R_3 is $CONR_8R_9$ (IC).

e) Wittig reaction of a 5-carboxy compound of formula I wherein R_3 is COR_7 (ID)

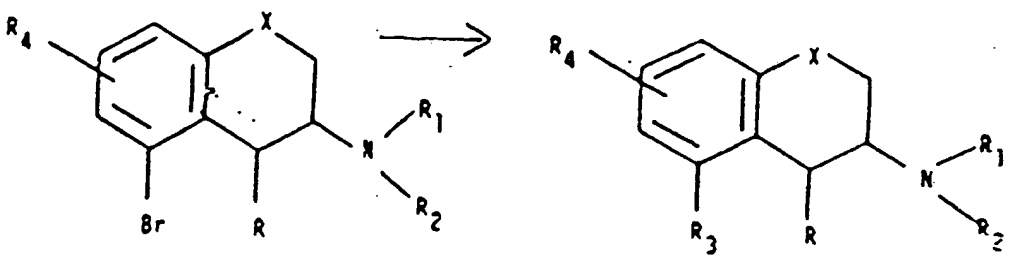


ID IE

and X, R, R_1, R_2 and R_4 are as defined under formula I and R_7 is alkyl, alkenyl or aryl by using a dipolar reagant to formation of a compound of formula I wherein R_3 is a C_2-C_6 alkenyl group, (IE).

f) catalytic hydrogenation of a compound of formula I wherein R_3 is a C_2-C_4 alkenyl group to obtain a compound of the formula I where R_3 is a C_1-C_6 alkyl group (IF).

g) substitution of a 5-bromochroman/thiochroman derivative

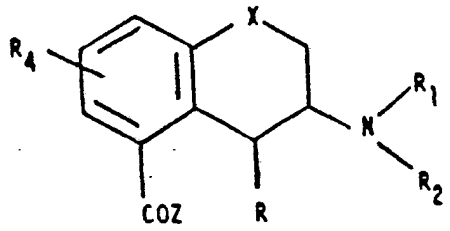


I

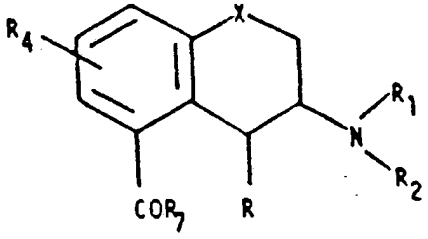
wherein X, R, R_1, R_2 and R_4 are as defined under formula I by treatment with a stannictrialkyl reagent in presence of

a zerovalent mental e.g. Pd° to obtain a compound of formula I wherein R_3 is C_1-C_6 alkyl, C_2-C_6 alkylen or aryl or in presence of carbonmonoxide formed a compound where R_3 is COR_7, where R_7 is C_1-C_6 alkyl, C_2-C_6 alkylen or aryl.

h) converting the 5-carboxychroman/thiochroman derivative of formula IA



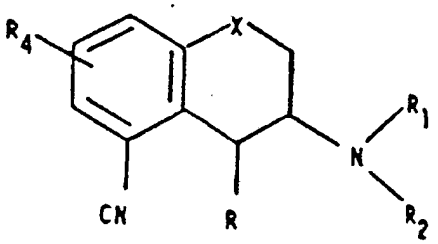
IA



ID

wherein X, R, R_1, R_2 and R_4 are defined as in formula I and Z is Cl, Br by using R_7Li to obtain corresponding compound of formula I when R_3 is COR_7 (ID) where R_7 is defined as C_1-C_6 alkyl, C_2-C_6 alkenyl or aryl;

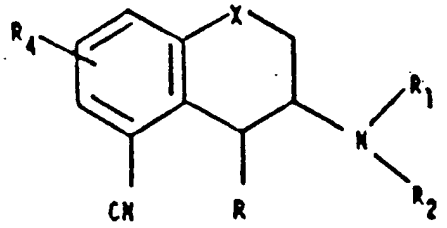
i) hydrolysis of a compound of formula I wherein R_3 is CN (IB)



IB

wherein X, R, R_1, R_2 and R_4 are as defined under formula I optionally followed by treatment with thionylhalide to obtain a compound of formula I wherein R_3 is COZ, where Z is OH, Cl or Br (IA)

j) substitution of a compound of formula I wherein R_3 is CN

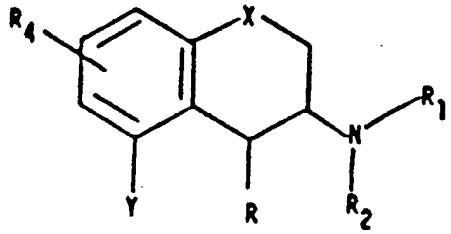


IB

wherein X, R, R_1, R_2 and R_4 are as defined under formula I by treatment with an organometallic reagent followed by hydrolysis to obtain a compound of formula I wherein R_3 is COR_7, where R_7 is C_1-C_6 alkyl, C_2-C_6 alkenyl or aryl (ID);

k) Hydrogeneration of a 5-alkene thiochroman/chroman derivative of formula I wherein R_3 is a C_2-C_6 alkenyl group by using H_2/Pd, H_2/Pt or H_2/Raney Ni or potassium azodicarboxylate to formation of corresponding thio-chroman/chroman derivative of formula I wherein R_3 is C_1-C_6 alkyl;

l) converting a compound of formula II

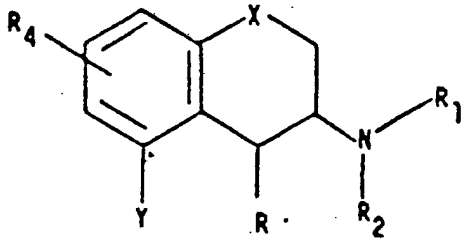


II

wherein Y is a leaving group and X, R, R_1, R_2 and R_4 are as defined under formula I by reaction with a transition metal, to form a ligand complex which undergoes an oxidative addition by treatment with a trialkylalkenyl-

stannane, to formation of a compound of formula I wherein R_3 is a C_2-C_6 alkenyl group.

m) converting a compound of formula II



II

wherein Y is a leaving group and X, R, R_1, R_2 and R_4 are as defined under formula I by a reaction with a transition metal to form a ligand complex, which undergoes an oxidative addition by treatment with a trialkylaryl stannane or aryl-boric acid reagants, to formation of a compound of formula I wherein R_3 is a 5-6-membered aryl which may contain 1 or 2 heteroatoms selected from N, O or S being either substituted or fused at two adjacent carbon atome; whereupon optionally a base obtained is converted to a acid addition salt or a salt obtained is converted to the base or to a different, acid addition salt, or optionally an isomeric mixture obtained is separated to a pure enantiomer.

27. Compounds, processes, pharmaceutical preparations, use of and method of treatment as claimed in any of claims 1-26 and substantially described.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 90/00863

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 311/58, 335/06, A 61 K 31/35, 31/38

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Chemical Abstracts, vol. 107, 1987, "Preparation of 3-aminodihydro/1/benzopyran and benzothiopyran derivatives as serotoninergic agonists", abstract 39617j, & JP 62 59273 (CIBA-GEIGY A.G.) see especially reg.no. 109140-40-1 --	1-23,26-27
X	J. Med. Chem., vol. 15, 1972, I.M. Lockhart et al: "3-Chromanamine Hydrochlorides with Central Stimulant Activity", pages 863-865 see the whole article --	1-2,6-23,26-27
X	EP, A2, 0222996 (CIBA-GEIGY AG) 27 May 1987, see especially pages 1-9 --	1-23,26-27
X	EP, A1, 0280269 (CIBA-GEIGY AG) 31 August 1988, see especially pages 1-5 --	1-23,26-27

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18th March 1991	1991 -03- 27
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Göran Karlsson

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	WO, A1, 8804654 (ASTRA LÄKEMEDEL AKTIEBOLAG) 30 June 1988, see especially pages 1-2 and 27-29 --	1-2,6-23,26-27

FURTHER INF RMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 24, 25 because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body, see rule 39.

2. [ ] Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 90/00863

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 91-02-28
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0222996	87-05-27	AU-B-	596113	90-04-26
		AU-D-	6231786	87-03-05
		JP-A-	62059273	87-03-14
EP-A1- 0280269	88-08-31	AU-D-	1234788	88-09-01
		JP-A-	63277671	88-11-15
		US-A-	4801605	89-01-31
		ZA-A-	8801375	88-08-29
WO-A1- 8804654	88-06-30	AU-D-	1082988	88-07-15
		EP-A-	0279150	88-08-24